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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,860	08/29/2001	Richard E. Rothman	001107.00185	5063

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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 07/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/940,860	ROTHMAN ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *23* is/are allowed.

6)☒ Claim(s) *2-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

NC

DETAILED ACTION

1. Applicants' response to the office action filed on May 12, 2005 has been entered.

Status

2. Claims 2-23 are pending. Claims 2 and 23 are amended. All arguments have been fully considered and thoroughly reviewed, and are deemed persuasive for the reasons that follow. This action is made FINAL necessitated by amendment.

New Grounds of Rejections necessitated by Amendment

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 2, 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Steinman (USPN. 5,516,292).

Steinman teaches a method for performing polymerase chain reaction of claim 2, comprising digesting reagents for polymerase chain reaction with a restriction endonuclease (see col. 3, line 1-40, col. 10, line 22-33), wherein the reagents comprise Amplitaq kit reagents (GENEAMP^{TM} PCR Kit reagents) which include Taq DNA polymerase, deoxynucleotide triphosphates (dNTPs) reaction buffer, and a pair of primers (see col. 11, line 37-44,col. 8, 29-36, col. 4, line 38-43, indicating the kit components). Inactivating said restriction endonuclease but not Taq DNA polymerase to form endonuclease-inactivated digested reagents (see col. 11, line 42-44); mixing a test sample and the endonuclease-inactivated digested reagents to form a

mixture and subjecting the mixture to conditions such that any templates present in the test sample hybridized to the primers are amplified (see col. 11, line 45-57, col. 12, line 1-16, indicates that the method follows the methods disclosed in col. 8, line 48-56 for PCR conditions for amplification of the target sample).

detecting amplification product, wherein the detected amplification indicates the presence of template, which hybridizes to both primers in the test sample (see col. 8, line 54-56).

With regard to claim 2, Steinman teaches that also teach restriction endonucleases will not digest primers and the restriction endonuclease is located in the interprimer region, which indicates the primers are have no restriction sites (see col. 9, line 49-54, col. 3, line 33-40, col. 4, line 46-50, indicating restriction sites in the interprimer region, see Fig 2(b) for inter primer region).

With regard to claim 4, Steinman teaches inactivation of restriction endonuclease but not Taq DNA polymerase (see col. 11, line 42-44, col. 4, line 1-3). Accordingly the instant claims are anticipated. Accordingly the instant claims are anticipated.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A. Claims 3, 8-10,15, 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steinman (USPN. 5,516,292) in view of DeFilippes (Biotechniques, Vol. 10, No. 1, pages 26, 28, 30, 1991).

Steinman teaches a method for performing polymerase chain reaction of claim 2, comprising digesting reagents for polymerase chain reaction with a restriction endonuclease (see col. 3, line 1-40, col. 10, line 22-33), wherein the reagents comprise Amplitaq kit reagents (GENEAMP™ PCR Kit reagents) which include Taq DNA polymerase, deoxynucleotide triphosphates (dNTPs) reaction buffer, and a pair of primers (see col. 11, line 37-44,col. 8, 29-36, col. 4, line 38-43, indicating the kit components). Inactivating said restriction endonuclease but not Taq DNA polymerase to form endonuclease-inactivated digested reagents (see col. 11, line 42-44); mixing a test sample and the endonuclease-inactivated digested reagents to form a mixture and subjecting the mixture to conditions such that nay templates present in the test sample hybridized to the primers are amplified (see col. 11, line 45-57, col. 12, line 1-16, indicates that the method follows the methods disclosed in col. 8, line 48-56 for PCR conditions for amplification of the target sample).

detecting amplification product, wherein the detected amplification indicates the presence of template, which hybridizes to both primers in the test sample (see col. 8, line 54-56).

With regard to claim 2, Steinman teaches that also teach restriction endonucleases will not digest primers and the restriction endonuclease is located in the interprimer region, which indicates the primers are have no restriction sites (see col. 9, line 49-54, col. 3, line 33-40, col. 4, line 46-50, indicating restriction sites in the interprimer region, see Fig 2(b) for inter primer region).

With regard to claim 4, Steinman teaches inactivation of restriction endonuclease but not Taq DNA polymerase (see col. 11, line 42-44, col. 4, line 1-3). Accordingly the instant claims are anticipated.

However Steinman did not specifically teach use of Alu I, and detection means and temperature conditions for inactivating the restriction enzyme.

DeFilippes teaches a method of performing polymerase chain reaction (PCR) comprising

(a) digesting reagents for PCR with a restriction endonuclease wherein the reagents comprise, reaction buffer, deoxynucleotide triphosphates and primers, template DNA which is a (see page 26, col. 3, line 34, page 28, col. 1, lines 1-3, paragraph 1 of Materials and methods section, Fig. 1-2); (b) inactivating said restriction endonuclease but not said Taq DNA polymerase (see page 28, col. 1, paragraph 1 of Materials and methods section); (c and d) mixing test sample and the reagents to form a PCR mixture and subjected to PCR amplification to form an amplified product (see page 28, col. 1, paragraph 1 of Materials and methods section); (e) detecting amplification product, which indicates the presence of target DNA in the test sample (see page 28, Fig. 1-2).

With regard to claim 3, DeFilippes teaches that the restriction endonuclease is Alu I (see page 28, Fig. 1-2);

With regard to claims 4 and 8, DeFilippes teaches the step of inactivating comprises heating to a temperature which inactivates restriction endonuclease but not Taq DNA polymerase at about 65 C for about 20 min (temperature at 90 C, for 20 min, about includes, 70, 80, or 90 C) (see page 28, col. 1, paragraph 1 of Materials and methods section);

With regard to claims 9-10, DeFilippes teaches that the detection step employs agarose gel and the product is labeled with ethidium bromide and visualized under UV light (see page 28, Fig. 1-2);

With regard to claim 15, 18, DeFilippes teaches that the method comprises amplifying amplification product using primers that hybridize to single 16S RNA species (within the template) (see page 28, col. 3, paragraph 1, Fig. 2).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method of performing PCR as taught by Steinman with a step of including temperature conditions, type of restriction enzymes such as Alu I and detection means and as taught by DeFilippes to achieve expected advantage of developing an improved and sensitive PCR method because DeFilippes explicitly taught that digestion of contaminating DNA with different restriction enzymes sutable for the target of interest would eliminate DNA contamination in PCR mixture (see page 26, col. 3, paragraph 1 under subtitle Introduction) An ordinary practitioner would have been motivated to modify the method of performing PCR with the incorporation of said additional steps as taught by DeFilippes to enhance sensitivity and efficiency of the PCR based detection method by minimizing contaminating DNA in PCR reactions and such modification of the method is considered obvious the cited prior art.

B. Claims 5-7, 11-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steinman (USPN. 5,516,292) in view of Hoshina et al. (USPN. (USPN. 5,571,674) .

Steinman teaches a method for performing polymerase chain reaction comprising digesting reagents for polymerase chain reaction with a restriction endonuclease (see col. 31-40, col. 10, line 22-33), wherein the reagents comprise Amplitaq kit reagents (GENEAMP^{TM} PCR Kit reagents) which include Taq DNA polymerase, deoxynucleotide triphosphates (dNTPs) reaction buffer, and a pair of primers (see col. 11, line 37-44,col. 8, 29-36, col. 4, line 38-43, indicating the kit components), wherein the primers have no restriction sites for the restriction endonuclease (see col.3, line 33-40, indicating restriction sites in the interprimer region, which means that the primers have no restriction sites and the restriction site is located with in the contaminating DNA which is flanked by the two primers);

Inactivating said restriction endonuclease but not Taq DNA polymerase to form endonuclease-inactivated digested reagents (see col. 11, line 42-44); mixing a test sample and the endonuclease-inactivated digested reagents to form a mixture and subjecting the miture to conditions such that nay templates present in the test sample hybridized to the primers are amplified (see col. 11, line 45-57, col. 12, line 1-16, indicates that the method follows the methods disclosed in col. 8, line 48-56 for PCR conditions for amplification of the target sample).

detecting amplification product , wherein the detected amplification indicates the presence of template which hybridizes to both primers in the test sample (see col. 8, line 54-56).

However, Steinman did not specifically teach the test sample comprising blood, a patient sample, urine, cerebral fluid, primers selected from eubacterial species specific DNA regions, identification of bacterial species by restriction digestion of amplification products.

Hoshina et al. of performing polymerase chain reaction (PCR) comprising

Mixing test sample and the PCR reagents, which include a primer pair to form a mixture (see col. 7, line 21-29, col. 17, line 66-67, col. 18, line 22-25) and subjecting the mixture to conditions such that any templates present in the test sample which hybridizes to said primer pair are amplified and detecting amplification product (see col. 7, line 29-37, col. 18, line 22-28).

With regard to claim 5, 11, Hoshina et al. teach that said sample is a treated blood sample and said treatment comprises extracting DNA therefrom (see col. 18, line 35-40, col. 7, line 21-29);

With regard to claim 6, Hoshina et al. teach that said blood sample from patients suspected of systemic bacteremia (see col. 20, line 22-53);

With regard to claim 7, Hoshima et al. teach primer sequence having (considered as open language as "comprising") the sequence as claimed in SEQ ID 1 (see sequence alignment).

With regard to claims 9-10, Hoshina et al. teach that said detection step employs gel electrophoresis and the amplification product is labeled with ethidium bromide and visualized under ultraviolet light (see col. 7, line 34-37);

With regard to claims 12-13, Hoshina et al. teach that said sample is obtained from urine and cerebrospinal fluid (See 18, line 35-43);

With regard to claims 14-15, Hoshina et al. teach that the development of primers hybridize to at eubacterial species' DNA in regions which are highly conserved and comprises 16S RNA genes (see col. 15, line 59-67, col. 16, line 1-6, col. 18, line 25-28, Figs.12-16);

With regard to claims 16-17, 21-22, Hoshina et al. also teach that the method further comprises identifying the bacterial species by sequencing the amplification product or by using restriction endonuclease digestion or restriction mapping that indicates use of one or more restriction endonucleases (see col. 7, line 34-52);

With regard to claim 18, Hoshina et al. teach that said method further comprises identifying a bacterial species by amplification of amplified product or amplification of templates in a test sample using primers selected from a single eubacterial species 16S RNA (see col. 19, line 54-67, col. 20, line 1-3, col. 21, line 23-43);

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine the method of amplification of a target nucleic acid as taught by Steinman with inclusion of the target biological samples to detect bacterial species as taught by Hoshina et al. to achieve expected advantage of developing a sensitive and enhanced method for detecting bacterial infections in biological samples. An ordinary skill in the art would have reasonable expectation of success that the inclusion of said target biological samples as taught by Hoshina et al. would result in an improved and sensitive method for detecting bacteremia in different biological samples such modification of the method is considered obvious the cited prior art.

Response to arguments:

5. With regard to the objection made in the previous office action, Applicants' amendment and arguments are fully considered and the objection is withdrawn in view of the amendment.

6. with regard to the rejection made in the previous office action under 35 USC 112, second paragraph, Applicants' amendment and arguments are fully considered and found persuasive. The rejection is withdrawn in view of the amendment.

7. with regard to the rejections made in the previous office action under 35 USC 103(a), Applicants' amendment and arguments are fully considered and the rejections are withdrawn in view of the amendment (the amendment reciting that both primers have no restriction sites, changed the scope of the claims) and arguments, and new grounds of rejections.

Conclusion

Claim 23 is free of prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
Examiner,
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER
7/19/05